Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US05/010125

International filing date: 25 March 2005 (25.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/556,391
Filing date: 25 March 2004 (25.03.2004)

Date of receipt at the International Bureau: 06 May 2005 (06.05.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

1314050

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APPLICATION NUMBER: *60/556,391*
FILING DATE: *March 25, 2004*
RELATED PCT APPLICATION NUMBER: *PCT/US05/10125*

Certified by

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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

Docket No.	PB60808P		

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	Number of Pages	13	**Total Number of Pages = 14**
☒ Abstract	Number of Pages	1	
☐ Drawings	Number of Sheets		☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. 19-2570	PROVISIONAL FILING FEE AMOUNT ($)	**$160.00**

Respectfully submitted,
Signature: Nora Stein-Fernandez Date: March 25, 2004

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☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

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20462

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Use

This invention relates to the use of the NK3 receptor antagonist talnetant [(S)-(-)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide] for treating bipolar disorder.

Talnetant, its preparation and its use in the treatment of pulmonary disorders, disorders of the central nervous system and neurodegenerative disorders are disclosed in published International Patent application WO 95/32948. Published International Patent applications WO 97/19927, WO 97/19928, WO 99/14196 and WO 02/094187 disclose additional therapeutic utilities for talnetant, pharmaceutically acceptable salts and processes for its preparation. The above-mentioned patent applications are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

There remains the need to identify further and improved medicaments of talnetant, particularly for the treatment or prevention of bipolar disorder.

According to a first aspect, the invention provides the use of talnetant, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment or prevention of bipolar disorder.

Suitable pharmaceutically acceptable salts of talnetant include basic salts with the appropriate acid for example organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids and the like. Preferably, talnetant is the free base. Talnetant may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. The invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Hereinafter talnetant, its pharmaceutically acceptable salts and solvates defined in the first aspect of the invention are referred to simply as talnetant.

The term bipolar disorder covers all variations and sub-categories of bipolar disorder, mania, hypomania, depressed episode, rapid cycling and manic depression, including without limitation, those categorised as shown below in the "Diagnostic and Statistical Manual of Mental Disorders" (DSM-IV-TR), Fourth Edition, edited by American Psychiatric Association:

296.00 Bipolar I Disorder, Single Manic Episode, Unspecified;
296.01 Bipolar I Disorder, Single Manic Episode, Mild;
296.02 Bipolar I Disorder, Single Manic Episode, Moderate;
296.03 Bipolar I Disorder, Single Manic Episode, Severe without Psychotic Features;
296.04 Bipolar I Disorder, Single Manic Episode, Severe with Psychotic Features;
296.05 Bipolar I Disorder, Single Manic Episode, In Partial Remission;
296.06 Bipolar I Disorder, Single Manic Episode, In Full Remission;
296.40 Bipolar I Disorder, Most Recent Episode Hypomanic;
296.40 Bipolar I Disorder, Most Recent Episode Manic, Unspecified;
296.41 Bipolar I Disorder, Most Recent Episode Manic, Mild;
296.42 Bipolar I Disorder, Most Recent Episode Manic, Moderate;
296.43 Bipolar I Disorder, Most Recent Episode Manic, Severe without Psychotic Features;
296.44 Bipolar I Disorder, Most Recent Episode Manic, Severe with Psychotic Features;
296.45 Bipolar I Disorder, Most Recent Episode Manic, In Partial Remission;
296.46 Bipolar I Disorder, Most Recent Episode Manic, In Full Remission;
296.50 Bipolar I Disorder, Most Recent Episode Depressed, Unspecified;
296.51 Bipolar I Disorder, Most Recent Episode Depressed, Mild;
296.52 Bipolar I Disorder, Most Recent Episode Depressed, Moderate;
296.53 Bipolar I Disorder, Most Recent Episode Depressed, Severe without Psychotic Features;
296.54 Bipolar I Disorder, Most Recent Episode Depressed, Severe with Psychotic Features;
296.55 Bipolar I Disorder, Most Recent Episode Depressed, In Partial Remission;
296.56 Bipolar I Disorder, Most Recent Episode Depressed, In Full Remission;
296.60 Bipolar I Disorder, Most Recent Episode Mixed, Unspecified;
296.61 Bipolar I Disorder, Most Recent Episode Mixed, Mild;
296.62 Bipolar I Disorder, Most Recent Episode Mixed, Moderate;

296.63 Bipolar I Disorder, Most Recent Episode Mixed, Severe without Psychotic Features;
296.64 Bipolar I Disorder, Most Recent Episode Mixed, Severe with Psychotic Features;
296.65 Bipolar I Disorder, Most Recent Episode Mixed, In Partial Remission;
296.66 Bipolar I Disorder, Most Recent Episode Mixed, In Full Remission;
296.80 Bipolar Disorder NOS; and
296.89 Bipolar II Disorder.

All recognised forms and variations of bipolar disorder mentioned herein are contemplated as within the scope of the present invention.

In addition to bipolar disorder, talnetant may be used in the treatment or prevention of major depressive disorders including the following: unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, the treatment of anxiety and the treatment of panic disorders. The term anxiety includes anxiety disorders, such as panic disorders with or without agoraphobia, agoraphobia, phobias, for example, social phobias or agoraphobia, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorders, generalised anxiety disorders, social anxiety disorders, acute stress disorders and mixed anxiety-depression disorders. Other mood disorders encompassed within the term major depressive disorders include dysthymic disorder with early or late onset and with or without atypical features, seasonal affective disorder, neurotic depression, post traumatic stress disorders, post operative stress and social phobia; dementia of the Alzheimer's type, behavioural disturbances in the elderly and Alzheimer's patients with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

Talnetant may be used in the treatment, maintenance of treatment or prevention of schizophrenia (including treatment in the prodrome phase) and schizophrenic

disorders including paranoid schizophrenia, disorganised schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, residual schizophrenia, schizophreniform disorder and schizoaffective disorders.

Talnetant may be used as an analgesic. In particular it may be used in the treatment or prevention of traumatic pain such as postoperative pain; traumatic avulsion pain such as brachial plexus; chronic pain such as arthritic pain such as occurring in osteo-, rheumatoid or psoriatic arthritis; neuropathic pain such as post-herpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia, fibromyalgia, causalgia, peripheral neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, AIDS related neuropathy, occipital neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, phantom limb pain; various forms of headache such as migraine, acute or chronic tension headache, temporomandibular pain, maxillary sinus pain, cluster headache; odontalgia; cancer pain; pain of visceral origin; gastrointestinal pain; nerve entrapment pain; sport's injury pain; dysmennorrhoea; menstrual pain; meningitis; arachnoiditis; musculoskeletal pain; low back pain e.g. spinal stenosis; prolapsed disc; sciatica; angina; ankylosing spondyolitis; gout; burns; scar pain; itch; and thalamic pain such as post stroke thalamic pain.

Talnetant may be used for the treatment of dysfunction of appetite and food intake and in circumstances such as anorexia, anorexia nervosa, obesity and bulimia.

Talnetant may be used for the treatment of sleep disorders including dysomnia, insomnia, sleep apnea, narcolepsy and circadian rhythmic disorders.

Talnetant may be used for the treatment or prevention of cognitive disorders. Cognitive disorders include dementia, mild cognitive impairment, amnestic disorders and cognitive disorders not otherwise specified.

Talnetant may be used as a memory and/or cognition enhancer in healthy humans with no cognitive and/or memory deficit.

Talnetant may be used for the treatment of tolerance to, dependence on and craving for a number of substances. For example, it is useful in the treatment of dependence on nicotine, alcohol, caffeine, phencyclidine (phencyclidine like compounds), or in the

treatment of tolerance to and dependence on opiates (e.g. heroin, morphine), cannabis or benzodiazepines; in the treatment of cocaine, sedative hypnotic, amphetamine or amphetamine- related drugs (e.g. dextroamphetamine, methylamphetamine) addiction or a combination thereof.

Talnetant may be used as an anti-inflammatory agent. In particular it may be used in the treatment of inflammation in asthma, influenza, chronic bronchitis and rheumatoid arthritis; in the treatment of inflammatory diseases of the gastrointestinal tract such as Crohn's disease, postoperative gastric ileus (POI), ulcerative colitis, inflammatory bowel disease (IBD) and non-steroidal anti-inflammatory drug induced damage; inflammatory diseases of the skin such as herpes and eczema; inflammatory diseases of the bladder such as cystitis and urge incontinence; and eye and dental inflammation.

Talnetant may be used for the treatment of allergic disorders, in particular allergic disorders of the skin such as urticaria, and allergic disorders of the airways such as rhinitis.

Talnetant may be used for the treatment of emesis, i.e. nausea, retching and vomiting. Emesis includes acute emesis, delayed emesis and anticipatory emesis. Talnetant is useful in the treatment of emesis however induced. For example, emesis may be induced by drugs such as cancer chemotherapeutic agents such as alkylating agents, e.g. cyclophosphamide, carmustine, lomustine and chlorambucil; cytotoxic antibiotics, e.g. dactinomycin, doxorubicin, mitomycin-C and bleomycin; anti-metabolites, e.g. cytarabine, methotrexate and 5- fluorouracil; vinca alkaloids, e.g. etoposide, vinblastine and vincristine; and others such as cisplatin, dacarbazine, procarbazine and hydroxyurea; and combinations thereof; radiation sickness; radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; poisons; toxins such as toxins caused by metabolic disorders or by infection, e.g. gastritis, or released during bacterial or viral gastrointestinal infection; pregnancy; vestibular disorders, such as motion sickness, vertigo, dizziness and Meniere's disease; post-operative sickness; gastrointestinal obstruction; reduced gastrointestinal motility; visceral pain, e.g. myocardial infarction or peritonitis; migraine; increased intercranial pressure; decreased intercranial pressure (e.g. altitude sickness); opioid analgesics, such as morphine; and gastro-oesophageal reflux disease, acid indigestion, over-indulgence of food or drink, acid stomach, sour

stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn and dyspepsia.

Talnetant may be used for the treatment of gastrointestinal disorders such as irritable bowel syndrome (IBS); skin disorders such as psoriasis, pruritis and sunburn; vasospastic diseases such as angina, vascular headache and Reynaud's disease; cerebral ischeamia such as cerebral vasospasm following subarachnoid haemorrhage; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders related to immune enhancement or suppression such as systemic lupus erythematosus and rheumatic diseases such as fibrositis; and cough.

Talnetant may be used for the treatment of neurotoxic injury which follows cerebral stroke, thromboembolic stroke, hemorrhagic stroke, cerebral ischemia, cerebral vasospam, hypoglycemia, hypoxia, anoxia or perinatal asphyxia cardiac arrest.

For the treatment of bipolar disorder, talnetant may be administered as monotherapy or in combination with at least one mood stabilising or antimanic agent. Examples of mood stabilising or antimanic agents that are useful in such combinations include those therapeutic agents known specifically for their mood stabilising or antimanic properties, such as lithium, but also include anti-convulsants having mood stabilising or antimanic properties, such as lamotrigine, gabapentin, topirimate, valproate or carbamazepine, and certain neuroleptic (including typical antipsychotic and atypical antipsychotic) agents having mood stabilising or antimanic properties, including butyrophenones, such as haloperidol, pimozide, and droperidol; phenothiazines, such as chlorpromazine, thioridazine, mesoridazine, trifluoperazine, perphenazine, fluphenazine, thiflupromazine, prochlorperazine, and acetophenazine; thioxanthenes, such as thiothixene and chlorprothixene; thienobenzodiazepines; dibenzodiazepines, such as clozapine; benzisoxazoles; dibenzothiazepines; imidazolidinones; benzisothiazolyl-piperazines; dibenzoxazepines, such as loxapine; dihydroindolones, such as molindone; aripiprazole; and derivatives thereof that have antipsychotic activity. Particularly preferred mood stabilising or antimanic agents for use in the combinations are lamotrigine, valproate, gabapentin, topiramate, oxcarbazepine, carbamazepine, olanzapine, risperidone, quetiapine, aripiprazole, haloperidol, clozapine, ziprasidone and lithium.

Particular advantages associated with combinations include equivalent or improved efficacy at doses of administration which are lower than those commonly used for the individual components where they are known for the treatment of bipolar disorder. The combinations may also provide advantages in treatment of patients who fail to respond adequately or who are resistant to treatment with certain mood stabilising or antimanic agents which are known for the treatment of bipolar disorder.

The combinations are preferably administered adjunctively. By adjunctive administration is meant the coterminous or overlapping administration of each of the components in the form of separate pharmaceutical compositions or devices. This regime of therapeutic administration of two or more therapeutic agents is referred to generally by those skilled in the art and herein as adjunctive therapeutic administration; it is also known as add-on therapeutic administration. Any and all treatment regimes in which a patient receives separate but coterminous or overlapping therapeutic administration of talnetant and at least one mood stabilising or antimanic agent are within the scope of the current invention. In one embodiment of adjunctive therapeutic administration as described herein, a patient is typically stabilised on a therapeutic administration of one or more of the of the components for a period of time and then receives administration of another component.

The combinations may also be administered simultaneously. By simultaneous administration is meant a treatment regime wherein the individual components are administered together, either in the form of a single pharmaceutical composition or device comprising or containing both components, or as separate compositions or devices, each comprising one of the components, administered simultaneously. Such combinations of the separate individual components for simultaneous combination may be provided in the form of a kit-of-parts.

Preferably in accordance with invention, talnetant is administered orally, which will typically involve swallowing so that the compound enters the GIT. Dosage forms for oral administration include solid formulations such as tablets, capsules containing particulates or powders, sachets, vials, powders, granules, lozenges, reconstitutable powders and liquid preparations (such as suspensions, emulsions and elixirs).

Oral dosage forms of talnetant may contain further excipients such as binding agents (for example syrup, acacia, gelatin, sorbitol and tragacanth); fillers (for example

lactose, sugar, maize-starch, calcium phosphate, sorbitol and glycine); tabletting lubricants (for example magnesium stearate); and disintegrants (for example starch, sodium starch glycollate and microcrystalline cellulose). In addition, the oral dosage form may contain preservatives, anti-oxidant, flavours, granulation binders, wetting agents and colourants.

Preferably the dosage form for oral administration is a tablet. Tablets may be prepared using standard technology familiar to the formulation chemist, for example by direct compression, granulation, melt congealing and extrusion. The tablet may be coated or uncoated. The tablet may be formulated to be immediate or controlled release. Controlled release formulations include delayed-, sustained-, pulsed or dual-release. Suitable tabletting excipients are described in the *Handbook of Pharmaceutical Excipients*, Pharmaceutical Press, 1986, published by The American Pharmaceutical Association and The Royal Pharmaceutical Society of Great Britain. Typical tabletting excipients include: carriers (for example lactose and starch), lubricating agents (for example magnesium stearate), binding agents, wetting agents, colorants, flavourings, glidants and disintegrants (for example croscarmellose sodium).

Excipients suitable for preparing liquid dosage forms include: suspending agents (for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel and hydrogenated edible fats); emulsifying agents (for example lecithin, sorbitan monooleate and acacia); aqueous or non-aqueous vehicles, which include edible oils (for example almond oil and fractionated coconut oil), oily esters (for example esters of glycerine and propylene glycol), ethyl alcohol, glycerine, water and normal saline; preservatives (for example methyl, propyl p-hydroxybenzoate and sorbic acid); and if desired conventional flavouring or colouring agents.

The effective dose of talnetant depends on the condition of the patient, the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg of talnetant, preferably 30 to 500 mg, most preferably 200 or 400 mg. The unit dose may be administered one or more times per day (for example 2, 3 or 4 times per day). The total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

Alternatively, for acute control of symptoms, talnetant may be administered by injection (for example intravenously, intravascularly, intramuscularly, subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain excipients such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative.

For long term control of symptoms, talnetant may be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously) or by intramuscular injection. For example talnetant may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins or as sparingly soluble derivatives for example as a sparingly soluble salt.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

It will be appreciated that the invention includes the following further aspects. The preferred embodiments described for the first aspect extend these further aspects:

i) a method of treating or preventing bioplar disorder by administration of talnetant;

ii) talnetant for use in treating or preventing bipolar disorder.

Example

The following patient study may be performed to show the efficacy of talnetant in treating bipolar disorder. This study is for illustrative purposes and is not intended to limit the scope of the invention in anyway.

This example study is a multicentre, double-blind, randomized, parallel, placebo-controlled, 3-week inpatient comparison of talnetant and placebo in subjects with

Bipolar I Disorder (in a recurrent manic or mixed episode). To be eligible for enrolment, a subject must meet inclusion/exclusion requirements including: 1) having a diagnosis of Bipolar I Disorder and currently experiencing a Recurrent Manic or Mixed Episode (Appendices A and B, respectively as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) and based on the modified Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) and 2) having a minimum of 20 on the YMRS. The study will last up to 42 days and will consist of 3 phases: a Screen Phase (2-7 days), a Treatment Phase (21 days), and a Follow-up Phase (14 days). After giving informed consent, completing the screening assessments, and meeting the inclusion/exclusion criteria, all subjects will enter a 2-7 day Screen Phase during hospitalisation. This Phase will function: 1) as a washout period for other medications (if required) and 2) to discontinue subjects who do not continue to satisfy inclusion/exclusion criteria (e.g., based on clinical laboratory, physical examination, and/or ECG results). Following completion of the Screen Phase, subjects who continue to satisfy the inclusion/exclusion requirements will enter the 21-day Treatment Phase. The subjects will be randomised 1:1 to one of two treatment groups: 200 mg talnetant or placebo. The first dose of study medication will begin on the morning of Day 1 of the Treatment Phase. During the Treatment Phase, assessments will be conducted on Days 4, 7, 10, 14, 17, and 21. Subjects will remain in the hospital until the Day 7 assessments are completed. Subjects may leave the hospital anytime after completion of the Day 7 assessments if, in the Investigator's clinical judgement, they are ready for discharge and meet the community standards for level of functioning as an outpatient. Subjects who leave the hospital before Day 7 for any reason will be discontinued from the Treatment Phase, and study medication will be discontinued. The Follow-up Phase will permit safety to be assessed 14 days after the last dose of study medication. Efficacy will be assessed by using the YMRS, 21-item HAMD, CGI-S, CGI-I, and the GAF. Safety of the treatments will be evaluated by assessing vital signs, weights, clinical laboratory measures, ECGs, physical examinations, and adverse events.

Claims

1. The use of talnetant, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment or prevention of bipolar disorder.

2. The use according to claim 1 wherein talnetant is the free base.

3. The use according to any preceding claim wherein the category of bipolar disorder (as categorised in the "Diagnostic and Statistical Manual of Mental Disorders" (DSM-IV-TR), Fourth Edition, edited by American Psychiatric Association) is selected from the list:

296.00 Bipolar I Disorder, Single Manic Episode, Unspecified;
296.01 Bipolar I Disorder, Single Manic Episode, Mild;
296.02 Bipolar I Disorder, Single Manic Episode, Moderate;
296.03 Bipolar I Disorder, Single Manic Episode, Severe without Psychotic Features;
296.04 Bipolar I Disorder, Single Manic Episode, Severe with Psychotic Features;
296.05 Bipolar I Disorder, Single Manic Episode, In Partial Remission;
296.06 Bipolar I Disorder, Single Manic Episode, In Full Remission;
296.40 Bipolar I Disorder, Most Recent Episode Hypomanic;
296.40 Bipolar I Disorder, Most Recent Episode Manic, Unspecified;
296.41 Bipolar I Disorder, Most Recent Episode Manic, Mild;
296.42 Bipolar I Disorder, Most Recent Episode Manic, Moderate;
296.43 Bipolar I Disorder, Most Recent Episode Manic, Severe without Psychotic Features;
296.44 Bipolar I Disorder, Most Recent Episode Manic, Severe with Psychotic Features;
296.45 Bipolar I Disorder, Most Recent Episode Manic, In Partial Remission;
296.46 Bipolar I Disorder, Most Recent Episode Manic, In Full Remission;
296.50 Bipolar I Disorder, Most Recent Episode Depressed, Unspecified;
296.51 Bipolar I Disorder, Most Recent Episode Depressed, Mild;
296.52 Bipolar I Disorder, Most Recent Episode Depressed, Moderate;

296.53 Bipolar I Disorder, Most Recent Episode Depressed, Severe without Psychotic Features;
296.54 Bipolar I Disorder, Most Recent Episode Depressed, Severe with Psychotic Features;
296.55 Bipolar I Disorder, Most Recent Episode Depressed, In Partial Remission;
296.56 Bipolar I Disorder, Most Recent Episode Depressed, In Full Remission;
296.60 Bipolar I Disorder, Most Recent Episode Mixed, Unspecified;
296.61 Bipolar I Disorder, Most Recent Episode Mixed, Mild;
296.62 Bipolar I Disorder, Most Recent Episode Mixed, Moderate;
296.63 Bipolar I Disorder, Most Recent Episode Mixed, Severe without Psychotic Features;
296.64 Bipolar I Disorder, Most Recent Episode Mixed, Severe with Psychotic Features;
296.65 Bipolar I Disorder, Most Recent Episode Mixed, In Partial Remission;
296.66 Bipolar I Disorder, Most Recent Episode Mixed, In Full Remission;
296.80 Bipolar Disorder NOS; and
296.89 Bipolar II Disorder.

Abstract

This invention relates to the use of the NK3 receptor antagonist talnetant [(S)-(-)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide] for treating bipolar disorder.